REMARKS

Claims 1-12 and 19-22 are pending in this application. By this Amendment, claims 1, 10, 11 and 12 are amended. No new matter is added.

Section 112, second paragraph, rejection

The Office Action rejects claims 10-12 under 35 U.S.C. § 112, second paragraph, as being indefinite. Applicants believe that this rejection is overcome with the above amendments to claims 10-12. Reconsideration and withdrawal of the rejection of claims 10-12 under 35 U.S.C. § 112, second paragraph, are thus respectfully requested.

Section 102/103 Rejections

The technical problem of the present invention was to find complexes of polydeoxyribonucleotides with cationic liposomes that would be stable in aqueous solution as medicaments (see lines 3-6 of page 2 of the present specification), for use in particular as anti-inflammatory drugs (see the above lines and the sentence between lines 17-18 of page 2) so that the aqueous emulsions containing the complexes of the invention could be used for subsequent treatments and also for long lasting administrations such as infusion (see the sentence bridging pages 4-5 of the specification).

Applicants have found that the liposome complexes according to the presently claimed invention with depolymerized polydeoxyribonucleotides having a molecular weight between 7,000 and 60,000 preferably 15,000 and 60,000, solve the above-discussed technical problem.

The improved stability of the liposome complex of the presently claimed invention is shown in Tables I-III on pages 27-29 of the present specification, wherein it is shown that in comparison to the prior art liposomes-polydeoxyribonucleotide complexes, wherein the same polydeoxyribonucleotides are encapsulated into the liposome, those of the presently claimed invention achieve a remarkable stability over the storage time of the experiment (30 days).

In contrast, the prior art liposome complexes lose at least 70% of their pharmacological activity over the same period of time.

To establish obviousness, there must be some motivation in the cited prior art wherein it is indicated how to solve the above technical problem, i.e., improved stability of said complexes over time for that it concerns anti-inflammatory, activity.

The Examiner was not able to find any passage in the prior art concerning the solution found.

Therefore, the presently claimed invention is novel and would not have been obvious.

The prior art liposomes were prepared according to ex. 2 comp. on page 15 of the present specification. The preparation was according to the F.C. Szoka et al. reference [7] mentioned in Gursoy.

A copy of the paper of F.C. Szoka et al., Proc. Natl. Acad. Sci. USA vol. 75, 9, pp 4194-4198, is attached hereto for the Examiner's reference.

The preparation process in said paper is disclosed in detail in the paragraph: "Preparation of reverse-phase evaporation vesicles" on page 4195, up to the sentence bridging the right-left columns of said page.

According to said method, the lipid mixture, after a first evaporation step, is dissolved in an organic solvent to increase the liposome solubility, and admixed with an aqueous phase containing the compound to be encapsulated.

The two-phase system is sonicated briefly until the mixture becomes a homogeneous opalescent dispersion. The organic phase is then removed on a rotary evaporator.

In this way, a liposome encapsulating the compound is obtained. See also the last lines of the abstract on page 4194.

The process used by Applicants for preparing the liposomes having the polydeoxyribonucleotides located on the outer surface of the vesicle differs from that described in the Szoka et al. reference since there is no sonication step.

In fact, it had been known that without sonication no encapsulation is possible.

The process used by Applicants is similar to that described in the paper of Y. Xu and F.C. Szoka, Biochemistry 1996. 35, pages 3616-3623, a copy of which is attached hereto for the Examiner's reference.

On page 5617, left column, under the paragraph "Materials and methods" it is reported a process for preparing liposome complex by mixing equal volumes of the aqueous solutions of the liposome and of the DNA, without sonication. It is noted that a complex is therein formed and that it can be also negatively charged, depending on the quantity of added DNA.

That means that DNA is on the outer surface, since a complex wherein DNA is included, bears always the charge given by the outer liposome layer, i.e., a positive charge in the case of using a cationic liposome, as in the present case.

In the inclusion complexes therefore, the net complex charge cannot be varied, as instead it happens for the liposome complex wherein DNA is on the outer surface.

In the method used by Applicants, a further step has been added, since the liposome aqueous phase was not used as such but was liophylized before addition of the polydeoxyribonucleotide solution. See step c) in the liposome complex preparation method at page 9 of the specification.

The Office Action rejects claims 1-12, 19 and 22 under 35 USC § 102(b) (paragraphs 2-4 on pages 2-3 of the Office Action) as being anticipated by Gursoy (Pharmazie, 1993). This rejection is traversed.

Applicants respectfully note that claims 1-12 are directed to the liposomes complexes; claim 19 is directed to a method of treatment inflammation and claim 2 to a method for providing a sustained release of prostacyclin.

The Office Action bases the rejection on the following assertion: Gursoy discloses cationic liposomes containing defibrotide in claimed amounts and the composition's anti-inflammatory activity.

Applicants' remarks are the following.

Gursoy teaches the preparation of a liposome complex with defibrotide, that is a polydeoxyribonucleotide obtained by depolymerization of high molecular weight DNA.

Gursoy teaches the preparation of liposomes encapsulating the polydeoxyribonucleotides, since it makes reference to the above commented paper of Zsoka. See reference [7] cited under the paragraph "Experimental - I. Preparation of liposomes", the sentence bridging pages 549-550.

The Office Action rejects claims 1-12, 19 and 22 under 35 U.S.C. 103 as being obvious over Gursoy (paragraphs 5-6 on pages 3-43 of the Office Action). This rejection is traversed.

The Office Action has considered the present invention obvious over Gursoy, on the following grounds:

- For the weight range of the components. This seems to apply in particular to claim 12.
- For the antithrombotic activity of the complex. This seems to apply in particular to claim 20.
- For the liposome complex being administered to humans. This seems to refer to claim 1.

Applicants respectfully submit that the presently claimed invention would not have been obvious over Gursoy, since on the basis of Gursoy it could not be said that a liposome complex prepared according to the method described in the invention, wherein the polydeoxyribonucleotides are bound on the outer surface of the liposome, could be more stable in aqueous solution than the complex wherein the same polydeoxyribonucleotides are encapsulated in the liposome.

Gursoy in fact is not aware of the technical problem of the stability of defibrotide-liposome complexes. Therefore there is no suggestion that would have directed the skilled to the solution found in the present invention.

Therefore, being no teaching or suggestion in Gursoy that would have directed the skilled to the solution found in the present invention to the technical problem of the

stability in water of the liposome-polydeoxyribonucleotide complexes, the presently claimed invention would not have been obvious over Gursoy.

The Office Action rejects claims 19-22 under 35 U.S.C. § 103(a), as being unpatentable over Gursoy in view of the Applicant's statements of the prior art and viceversa.

Claims 19-22 are method claims.

This obviousness rejection appears to be based on the following issue: Since the Applicant has indicated on page 4 of the specification the activity of defibrotide in the claimed diseases, in view of the improved efficacy in inflammation of the Gursoy complex, it would have been obvious to use said complex also for the other diseases for which defibrotide is used.

Applicants respectfully submit that this rejection has nothing to do with the technical problem of the present invention and the solution found by the Applicant.

This rejection refers to a well known effect of drug-liposome complexation that has nothing to do with the technical problem of the present invention.

In fact, the assertion in the Office Action could be as well applied to the Gursoy liposome complexes, which as shown in the examples of the present specification do not instead solve the technical problem of the present invention.

On the basis of Gursoy and Applicants statements of the prior art, or viceversa, the skilled could have not guessed that the complex of the invention could be more stable than that of Gursoy, and therefore the former could allow preparation of formulations having a long-lasting activity.

The Office Action also rejects claims 1-12 and 19-22 under 35 U.S.C. § 103(a) as being unpatentable over Applicant's statements of prior art in combination with Litzinger by itself, or in further combination with Maccarone, Eastmann, individually or in combination (paragraph 8, pages 4-6 of the Office Action). This rejection is traversed.

The Office Action asserts that "Applicant indicates that on pages 3-7 of the specification, it is stated that the instant polydeoxyribonucleotides are known for their function." (see the last lines on page 4 of the Office Action).

Applicants respectfully submit that the fact that the instant polydeoxyribonucleotides are known for their function would not have directed the skilled to the solution found in the present invention to the technical problem of finding stable polydeoxyribonucleotide-liposome complexes. In fact, in the applied art there is no hint to solve the technical problem of the present invention.

The Office Action further asserts that "Litzinger teaches that oligonucleotides have the inability to efficiently traverse through cellular membranes and hence complexation with cationic liposomes" (see the first sentence of page 5 of the Office Action).

Applicants respectfully submit that the issue is not the circumstance that polydeoxyribonucleotides form complexes with cationic liposomes, but rather the stability of said complexes.

Applicants have prepared and have attached hereto a Declaration signed by the Inventor R. Porta.

The Declaration declares that the stability in water of a liposome complex prepared with the method of the present invention has been studied, wherein the

depolymerized polydeoxyribonucleotides are located on the outer surface of the liposomes, but the molecular weight is of 90,000, therefore higher than the present molecular weight limits of claim 1.

Therefore said complex, apart for the molecular weight of the polydeoxyribonucleotides, has been prepared as those recited in claim 1.

In the stability test performed in the Declaration also a polydeoxyribonucleotide complex according to the present invention (polymer M.W. = 50,000) has been assayed.

The data reported in Table 1 of the Declaration indicated that during the period of said stability test (3 weeks) the liposome complex with polymer M.W. = 90,000 was not found stable, while that with polymer M.W. 50,000 was stable.

Applicants respectfully submit that the results achieved in the test reported in the Declaration further demonstrates that the present invention is completely unexpected over the prior art.

In fact Litzinger is completely silent on the issue that stability of the liposome complexes should depend on the molecular weight of the polydeoxyribonucleotide.

The liposome complexes of the present show improved stability not only in the liposome complexes where the same polydeoxyribonucleotides are encapsulated (Gursoy), but also in liposome complexes, prepared with the method of the present invention, wherein the polydeoxyribonucleotides have a molecular weight higher than the present limits.

Therefore, in view of Litzinger the skilled could not have find out the solution to the technical problem of the present invention.

Therefore, also the further proposed combination of Litzinger and Applicants' statements of prior art (pages 3-7 of the present specification) would not have provided the skilled any more help for solving the technical problem of the present invention.

The Office Action asserts that "Maccarone teaches that DNA when complexed with cationic liposomes are able to transfect protoplast." (see the 2nd period on page 5 of the Office Action).

Applicants note that the disclosure that DNA when complexed with cationic liposomes are able to transfect protoplast would not have helped the skilled, for the same reasons herein above stated for Litzinger, in solving the technical problem of the present invention.

Neither the combination of Maccarone + Litzinger, or Maccarone + Litzinger + Applicants' statements of prior art are relevant, since none of said documents should be considered a pertinent prior art for the reasons given above.

The Office Action asserts that "Eastmann teaches that the complex prepared by addition of cationic liposomes and DNA has an efficient transfection ability." (see the 3rd period on page 5 of the Office Action).

In the Abstract of Eastmann it is referred that the problem at issue therein is gene therapy by aerosol, and Eastmann notes that aerosol delivery of transgenes using cationic lipids is currently limited.

The same comments made above for Litzinger and Maccarone apply to Eastmann and for the same reasons Eastmann should not be considered as a pertinent prior art.

The combination of Eastmann with any or all of the preceding references doe not add anything more that considering Eastmann alone.

The references cited by the Examiner are not relevant to the present invention, because the references state that complexation is required for oligonucleotides to achieve pharmacological activity (i.e. transfection ability) and the claimed polydeoxyribonucleotides obtained by depolymerization of nucleic acids are effective even without complexation.

The Office Action has asserted the following:

- That the instant claims do not recite any specific amount or ranges for the nucleotides.
- That "Pharmaceutique OMS" shows that defibrotide does not have mutagenic potential in the bacterial system and therefore does not posses transfection capability.

The Office Action further asserts that if the cationic liposomes have the ability to increase the transfection of molecules which normally do not enter cells, then one of ordinary skill in the art would reasonably expect to increase the transfection of the claimed oligonucleotides by liposomes.

Regarding the assertion that Applicants' remarks that the technical problem is the stability of the liposome complex, Applicants have found that a specific range of molecular weight of depolymerized polydeoxyribonucleotides, not specific amounts of nucleotides, is critical for said stability.

Regarding the second assertion, Applicants note that by the term "transfection", see in Maccarone page 1417, first full sentence under the Summary, it is meant the

introduction of exogenous genes into eukaryotic cells. See for further confirmation the definition of transfection given in the enclosed page 144 from the book : "Glossary of Biotechnology terms".

Said otherwise according to the references is the gene that is transfected, and it is not possible that a DNA could acquire genetic properties by transfection.

Therefore it is respectfully submitted that, contrary to what is asserted in the Office Action, one of ordinary skill in the art would not have reasonably expected to increase the transfection of the claimed oligonucleotides by liposomes since the claimed oligonucleotides, as demonstrated by "Pharmaceutique OMS", are not mutagen, therefore they are not genes ab initio.

Therefore, also on said grounds Litzinger, Maccarone and Eastmann should not be considered pertinent prior art.

In view of the above, the rejections under 35 U.S.C. § 102(b) and § 103(a) are untenable and reconsideration and withdrawal thereof are respectfully requested.

Conclusion

Applicants respectfully submit that this application is in condition for allowance and such action is earnestly solicited. If the Examiner believes that anything further is desirable in order to place this application in even better condition for allowance, the Examiner is invited to contact Applicants' undersigned representative at the telephone number listed below to schedule a personal or telephone interview to discuss any remaining issues.

Should this response not be considered timely, Applicants petition for an appropriate extension of time. Please charge any fee deficiency or credit any overpayment to Deposit Account No. 01-2300, **referencing attorney docket number 108907-09014**.

Respectfully submitted,

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Attachments